Remarks

I. The Office Action

Claim 1 is pending, and stands rejected under the judicially created doctrine of obvious-type double patenting, and under 35 U.C.S §§ 112, second paragraph, 102(b) and 103(a). With this Reply, claim 1 is canceled and claims 2-35 are newly added. Applicants submit that the claims as presented above, in view of the comments that follow, are patentable over the prior art. Reconsideration of the claims as pending is respectfully requested.

II. Applicant's Invention

The present invention is directed to reverse thermally viscosifying composition including a block copolymer in an aqueous medium. The block copolymer includes a first polyoxyalkylene block having a hydrophobic region and a hydrophilic region and a second block comprising a bioadhesive polymer or oligomer. The polyoxyalkylene block effective to form micelles in solution in response to a change in temperature. The composition reversibly viscosifies at a temperature in the range of 22 to 40°C.

The present invention is also directed to a pharmaceutical composition including the above-mentioned block copolymer in an aqueous medium and an active agent which imparts a pharmaceutic or cosmetic effect. The composition viscosifies at a temperature in the range of about 22°C to about 40°C.

The present invention is also directed to methods of making a reverse thermally viscosifying block copolymer. The method includes providing an end-functionalized polyoxyalkylene having at least one terminal group that is reactive with vinyl(carboxylic acid), and reacting the end-functionalized polyoxyalkylene with a vinylcarboxylic acid in the presence of a polymerization initiator form a poly(vinylcarboxylic acid). The terminal group of the polyoxyalkylene forms a link to the poly(vinylcarboxylic acid.

III. Claim Amendments

Support for claims 2 and 3 is found on page 14, lines 12-29, where micelle formation of the polyoxyalkylene component of the block copolymer is described; on page 5, line 19, where a composition end-modified by a bioadhesive polymer is disclosed; and on page 11, lines 2-3, where reversible viscosification is disclosed.

Newly added claims 4-30 find support in the claims as originally filed.

Claims 31-35 find support in Examples set forth on pages 40-51. In particular, support for the reaction of a terminal group of an end-modified polyoxyalkylene with poly(vinyl acid) is found on page 41, lines 12-23; page 46, lines 6-7; and page 47, lines 20-27.

No new matter is introduced with amendment of the claims.

IV. Rejections under Section 112

Claim 1 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is canceled and the rejection is moot. Newly added claims 2-35 do not contain the perceived defects of previously presented claim 1. The rejection may now be withdrawn.

V. Rejection of the claims under obvious-type double patenting

Claim 1 stands rejected under the judicially created doctrine of obvious-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,316,011. Claim 1 is canceled and claims 2-34 are newly added.

The instant application is commonly owned with U.S. Patent No. 6,316,011. Upon indication of patentable subject matter, applicant will consider the appropriateness of filing a Terminal Disclaimer.

VI. Rejection of the claims over Hoffman

Claim 1 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Hoffman (WO 95/24430). A claim is anticipated only if each and every element of the claim is found, either expressly or inherently, in a single reference. MPEP § 2131. Applicants respectfully traverse the rejection.

Hoffman discloses block copolymers that include poloxamer (a form of polyoxyalkylene) and poly(acrylic acid). Hoffman teaches that each of these components must have a lower critical solution temperature (LCST) ranging from 20-40 °C at physiological pH. Hoffman does not teach or suggest a block copolymer "having a hydrophobic region and a hydrophilic region, said polyoxyalkylene block forming micelles in solution in response to a change in temperature," as is recited in claims 2-30.

A polyoxyalkylene having an LCST does not teach or suggest a polyoxyalkylene exhibiting micelle formation. An LCST is the temperature at which a polymer phase-separates from solution. Below the LCST the polymer is solvated and in solution, while above the LCST the polymer condenses and precipitates.[1] Transition between a swollen, solvated phase and a condensed, precipitated phase is an essential feature of the Hoffman composition. Hoffman relies on these changes in physical state to release the drug contained in the composition, noting that:

> "upon contact with the treatment area, the particles hydrate, swell and release drug during particle swelling and dissolution," page 8, lines 36-37;
>
> and again that:
>
> "upon contact with the treatment area, the pH-sensitive polymer component of the graft and block copolymers or hydrogels either hydrate or swell, or collapse, thereby causing release of drug from the copolymer drug mixtures," page 9, lines 29-32;
>
> and further that:

[1] An LCST may also be referred to as a cloud point (see page 2, line 29-31 of Hoffman). An LCST (cloud point) is confirmed by absorbance data (e.g., Fig. 19), indicating that the composition is no longer translucent above the LCST (that is, light is scattered by the sample particles).

"The temperature-sensitive polymer resists hydration and swelling of the mixture, thereby imparting a sustained and controlled release of the drug to the treatment area." Abstract.

In contrast, the composition of the present invention is directed to a block copolymer that does not have an LCST, but instead forms micelles in the physiological temperature range. See Figure 1 of the instant application. Because the micelles remain in solution, the polymer does not phase-separate, does not swell and collapse, and has no LCST (or cloud point) at physiological temperatures.

Polyoxyalkylene block copolymers that form micelles and those that have an LCST represent two different classes of materials. Exhibit 1 is a data sheet provided by BASF, a manufacturer of a large number of polyoxyalkylene block copolymers under the tradename "Pluronic®," which shows that the exemplary copolymers taught by Hoffman, namely Pluronics® L61, L92 and L122 (see Example 6), all have low oxyethylene content and all have cloud points, i.e., an LCST, at physiological temperatures. In contrast, an exemplary copolymer used in the instant compositions, Pluronic® F127, has a high oxyethylene content, no cloud point (LCST) up to 100 °C, and forms micelles at physiological temperatures. The gelling properties of polyoxyalkylenes are known. See, Exhibit 2.

The micelle-forming compositions of instant invention possess many unique advantages over the LCST materials of Hoffman. Because the composition does not precipitate, i.e., have a cloud point, at physiological temperatures, "it remains clear and translucent before and after the triggering event" (page 16, lines 15-16), and "hydrophobic domains are created which may be used to solubilize and control release of hydrophobic agents" (page 17, lines 5-7). Furthermore, the combination of bioadhesion and increased viscosity at body temperature allows the drug to remain in contact with the target tissue and to release slowly over an extended time (page 12, line 25 – page 13, line 1). These represent substantial new and non-obvious properties for the claim pharmaceutical compositions of the instant application.

With regard to method claims 31 through 35, Hoffman discloses a method of making a graft copolymer by reacting a functionalized temperature sensitive oligomer, e.g., poly(N-isopropylacrylamide), onto a functionalized pendant group of polyacrylic acid. See, Example 1

of Hoffman. There is no teaching or suggestion of linking an end-modified polyoxyalkylene with poly(vinyl acid) in the presence of a polymerization initiator.

In summary, the claimed invention is patentable over Hoffman because Hoffman neither teaches nor suggests a block copolymer comprising a polyoxyalkylene block having a hydrophobic region and a hydrophilic region that forms micelles in solution in response to a change in temperature and a second block comprising a bioadhesive polymer or oligomer. Furthermore, Hoffman does not teach or suggest of linking an end-modified polyoxyalkylene with poly(vinyl acid) in the presence of a polymerization initiator.

The rejection may be withdrawn.

VII. Rejection of the claims over Viegas

Claim 1 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Viegas (US 5,847,023). In order to establish a *prima facia* case of obviousness, the Examiner bears the burden of demonstrating that (1) there is some suggestion or motivation in the prior art to modify or combine the prior art teaching to obtain the claimed invention, (2) the prior art indicates that there is a reasonable expectation of success, and (3) the prior art references teach or suggest all the claim limitations. See MPEP §§ 2142 and 2143. Applicants respectfully traverse the rejection.

Viegas teaches an admixture of a polyoxyalkylene, such as the Pluronic® series of compounds available form BASF with an ionic polysaccharide. A counter-ion, e.g., Ca^{2+}, is added to the mixture to form a thermally irreversible gel.

There is no teaching of a block copolymer having a first polyoxyalkylene block having a hydrophobic region and a hydrophilic region that forms micelles in solution in response to a change in temperature, and a second block comprising a bioadhesive polymer or oligomer. Viegas is simply a mixture of two compounds. In contrast, the claimed compositions represent a

new chemical entity – a block copolymer in which a polyoxyalkylene block and a bioadhesive polymer block are chemically combined in a single molecule.[2]

Physical mixtures of different polymers in no way suggest the novel block copolymer compositions of the instant claims. Significantly, the compositions disclosed in Viegas are thermally irreversible gels, which represents a teaching away from the claimed reversibly viscosifying compositions. It is submitted that the claimed invention is patentable over the teachings of Viegas, and it is requested that the rejection be withdrawn.

VIII. Petition for Extension of Time

Applicants hereby Petition for a two month extension of time to extend the period for response for two months, up to and including September 23, 2003. Enclosed is a check in the amount of $570.00 to cover the cost of additional claims and the fee set forth in 37 C.F.R. § 1.17(b).

If there are any questions, please call the undersigned at the telephone number indicated below.

Respectfully submitted,

Date: September 23, 2003

Eyal S. Ron

MADASH LLP
7 Coach Road
Lexington, MA 02420
Tel. (617) 308-8200
Fax. (208) 730-5966

[2] Block polymers, by definition, are chemically linked to one another. A physical mixture of the individual polymers is not a block copolymer.